Power, expertise and the limits of representative democracy: genetics as scientific progress or political legitimization in carcinogenic risk assessment of pharmaceuticals?

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Abstract In modern ‘representative’ democratic states, the legitimacy of governments’ actions rests on their publicly declared commitment to protect the interests of their citizens. Regarding the pharmaceutical sector in most democracies, new drug products are developed and marketed by a capitalist industry, whose member firms, via shareholders, have commercial interests in expanding product sales. In those democracies, states have established government agencies to regulate the pharmaceutical industry on behalf of citizens. State legislatures, such as the US Congress and European Parliaments, have charged government drug regulatory agencies with the legal responsibility to protect public health. Yet, this paper argues that government drug regulatory agencies in the EU, Japan, and USA have permitted the pharmaceutical industry to reshape the regulatory guidance for carcinogenic risk assessment of pharmaceuticals in ways that are not techno-scientifically defensible as bases for improved, or even equivalent, protection of public health, compared with the previous techno-regulatory standards. By adopting the industry’s agenda of streamlining carcinogenicity testing in order to accelerate drug development and regulatory review, it is contended that these regulatory agencies have allowed the techno-regulatory standards for carcinogenic risk

assessment to be loosened in ways that are presented as scientific progress resulting from new genetics, but for which there is little evidence of progress in public health protection.

Introduction: industrial interests and state power in democracy and expertise

Science, capitalist industry and the state all pre-date modern democracy. Nonetheless, they all lay claim to the betterment of society. Since the ‘enlightenment’ period, science has been justified as a progressive force in society capable of improving the conditions of humanity, while the advancement of capitalist industry, it is claimed, is necessary to generate technological and economic improvements (Easlea 1973; Schumpeter 1942). States, for their part, have always had pretensions to look after their populations, but with the onset of modern ‘representative’ democratic states in the twentieth century, the legitimacy of governments’ actions has to some extent rested on their publicly declared commitment to protect the interests of their citizens.

Regarding the pharmaceutical sector, in particular, new drug products are developed and marketed by a capitalist industry, whose member firms, via shareholders, have commercial interests in expanding product sales. In advanced industrialised democracies, states have established government agencies to regulate the pharmaceutical industry on behalf of citizens. State legislatures, such as the US Congress and European Parliaments, have charged government drug regulatory agencies with the legal responsibility to protect the public interest in safe and effective pharmaceutical products (Abraham 1995; Abraham and Lewis 2000). The promise of technological improvement by the pharmaceutical industry satisfies the interests of patients and public health only when new drug products offer therapeutic/health benefits that

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outweigh their risks. When that is not the case, the interests of the industry and public health may diverge and conflict. The sciences of risk assessment, including toxicology, pharmacology, and pharmaco-epidemiology, have developed norms, methods, and standards to characterise drug risks. As this paper is concerned with the carcinogenic risk assessment of pharmaceuticals intended to treat non-life-threatening conditions, drug benefits need not detain us because no therapeutic benefit in treating a non-life-threatening condition could outweigh inducing cancer in patients with such a condition.

Fundamentally, therefore, it is in the interests of patients and public health to minimise the carcinogenic risk of pharmaceuticals. Insofar as government regulatory agencies are supposed to protect public health, then such minimization should also be the priority and responsibility of those regulatory bodies. Pharmaceutical companies' priority, however, is to enable their drug products to gain access to markets as quickly, cheaply, and extensively as possible. This may involve a motivation to reduce the costs and time associated with drug testing, including carcinogenic risk assessment, by lowering the standards of testing required of firms.

In this paper, we argue that government drug regulatory agencies in the EU, Japan, and USA have permitted the pharmaceutical industry to reframe the regulatory guidance for carcinogenic risk assessment of pharmaceuticals in ways that are not techno-scientifically defensible as bases for improved, or even equivalent, protection of patients and public health, compared with the previous techno-regulatory standards. Such 'policy reframing' has prescribed problem areas and shaped views about what counts as progress (Laws and Rein 2003). Specifically, by adopting the industry's agenda of streamlining carcinogenicity testing in order to accelerate drug development and regulatory review, we argue that these regulatory agencies have allowed the techno-regulatory standards for carcinogenic risk assessment to be loosened in ways that are presented as scientific progress resulting from new genetics, but for which there is little evidence of progressiveness in terms of public health protection.

New genetics technologies enabled rodents to be genetically manipulated in ways thought to make them more sensitive to human carcinogenic risks. For example, genes thought to be associated with human carcinogenesis could be introduced into mice. Such 'geneticisation' of carcinogenic risk assessment of pharmaceuticals facilitated the introduction of shorter in vivo carcinogenicity tests, lasting only about 6 months, in genetically engineered mice, as potential replacements for lifespan carcinogenicity studies of rodents, typically of 2 years duration. Thus, carcinogenic risk assessment derived from new genetics technologies had the potential to satisfy some of industry's interests in reducing drug development costs and time.

However, from the perspective of progress in protecting patients and public health from cancer risks, at stake was whether the new short-term in vivo tests could detect the type of carcinogens screened for by the life span studies.

The research for this paper involved a huge amount data collection and analysis. The paper has evolved from data collected for previous research projects and our involvement with the 'Genetics and Democracy' seminar series hosted by the University of Lund. One of the authors has been working in this field for over 15 years, with the two most intensive periods of fieldwork in the late 1990s and 2002–2005. Both documentary research and interviews methods were employed. In total, over 80 interviews were conducted with scientists and other officials in academia, industry and government, as well as representatives of consumer and public health advocacy organisations. Interviewees have been anonymised.

Background: political and techno-scientific context

For many decades, cancer has been, and remains, one of the major killers of people in industrialised countries. While cancer has many roots, it is well established that exposure to chemical carcinogens, including pharmaceuticals, is a significant contributory cause of cancer rates in populations. Consequently, drug regulatory agencies and scientists working in the pharmaceutical industry, and beyond, developed ways of testing new drugs to investigate whether or not they might pose carcinogenic risks to humans while taking drugs during clinical trials or after general market release.

When testing new drugs for carcinogenicity, regulators and industrial scientists have had to rely on the extrapolation of results from non-human tests because most carcinogenic risks accelerate over the lifespan—70–90 years for humans—far too long for clinical trials (Schou 1992, p. 210). Such human testing would also be unethical because it could only reveal that the test drug caused cancer by inducing cancer in a significant number of the trial participants. Accordingly, since the late 1960s, the two types of carcinogenicity studies developed have been: short-term in vitro mutagenicity tests, and life span in vivo studies in rodents (Hayashi 1994, p. 291). The former involves adding the test drug to mammalian/human cells or to micro-organisms in glass dishes in order to see if the chemical alters/damages DNA, causing mutations, associated with carcinogenic risk (King 1996, pp. 93–94). Pharmaceuticals found to damage DNA in vitro are genotoxic carcinogens, also known as mutagenic carcinogens. However, many cancer-inducing chemicals do so without damaging DNA as a primary biological activity (Purchase 1992). These *non-genotoxic* carcinogens (also

known as non-mutagenic carcinogens) are *not* detected by short-term mutagenicity tests (Ashby and Tennant 1991). Sometimes, this may be because a compound is not carcinogenic per se, but when administered to a whole live animal, it is metabolised into a carcinogenic substance.

Hence, in addition, animal models of human carcinogenesis have been employed to screen for non-genotoxic carcinogens by feeding rodents the test drug over (most of) their lifespan, usually between 18 and 24 months.¹ At the end of the study, the incidence and nature of the tumours found among the rodents given the test drug are compared with those in a ‘control group’ which do not receive the drug. However, because of the problem of extrapolating findings to another species, and to humans in particular, the World Health Organization (1969) recommended that life-span carcinogenicity testing should be conducted in *at least two species* (typically mice and rats) before being approved on to the market by government regulators. By the late 1970s, the regulatory agencies in North America, Western Europe, and Japan all accepted this view (Abraham 1998). One exception to this was acknowledged, namely the category of drugs developed to treat life-threatening diseases, especially where no satisfactory alternative therapy existed. To avoid delaying the availability of therapy to desperately ill patients, regulators reasonably took the view that long-term rodent carcinogenicity testing could be deferred to post-marketing for drugs intended to treat life-threatening conditions (D’Arcy and Harron 1996, p. 258).

In the overall non-clinical safety evaluation of a new drug, the lifespan carcinogenicity study in rodents consumes the most time and resources; taking over 3 years and costing over 1 million US dollars per compound tested (Abraham and Reed 2001). The results of these studies can have a major impact on the approval of a product (Contrera 1996). According to Monro (1996, p. 262), a representative of the US Pharmaceutical Research and Manufacturers Association (PhRMA), such a lengthy operation can be a major deterrent to some drug development programmes. To reduce the time and multi-million pound costs of bringing a new drug to market, the international pharmaceutical industry has sought ways of reducing drug development times (Halliday et al. 1997, p. 63).

For example, in the 1980s, the Association of the British Pharmaceutical Industry (ABPI) established the Centre for Medicines Research (CMR) to ‘monitor the regulatory process in different countries in order to provide data which will support recommendations to expedite this [drug testing] process’ (CMR 1995, p. 3). In particular, the Centre for Medicines Research and other elements within

the pharmaceutical industry questioned the relevance of findings from, and the predictive value of, rodent lifespan carcinogenicity tests for assessing human risk of cancer on the grounds that many chemicals found to provoke cancer in rodents did not seem to induce cancer in humans (Bentley et al. 1992). Some argued that carcinogenicity testing should focus more attention on the mechanisms of cancer induction, as these might be species-specific, while the Centre for Medicines Research declared one of its goals to be the *reduction of regulatory standards to just one lifespan carcinogenicity study in one rodent species* (Mulliger 1997, p. 16).

A key part of the strategy of reducing drug development times for the industry since the 1990s has been the international harmonisation of regulatory standards for drug testing, especially in the three largest markets of North America, Western Europe, and Japan. With internationally harmonised regulatory standards, pharmaceutical companies and government agencies are supposed to make efficiency gains because the former do not need to respond to inconsistent regulatory demands from different countries, and the latter do not duplicate regulatory workloads already conducted elsewhere. The most significant and highly influential institutional entity involved in such harmonisation is the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which comprises the three pharmaceutical industry associations and regulatory agencies of the EU, USA, and Japan. While the International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) acts as the secretariat of ICH, many of the key participants are industry and government scientists, who formed ‘expert working groups’ in areas of drug safety, quality, and efficacy with a view to harmonising related regulatory standards across the three regions at meetings throughout the 1990s and 2000s (IFPMA 2000). Ostensibly, a publicly declared guiding principle of ICH was that harmonisation should not compromise drug safety.

While a reduction in the time and resources required for non-clinical drug safety testing was clearly one motivation for ICH’s reviews of regulatory standards, the process was presented publicly and officially as one of technical science, as its name suggests. Moreover, participants were admitted to the process on the basis of technical expertise. Hence, not only was the ICH process an industry-regulator dialogue, excluding consumer organisations and public health advocacy groups, save a limited consultation effort (see below), it also treated the review and construction of regulatory standards for carcinogenic risk assessment purely as techno-scientific problem-solving. We suggest that such a representation was misleading because it concealed the socio-political motivations involved and because the constructions and interpretations of data within

¹ Some scientists refer to these life span carcinogenicity studies as ‘long-term’, rather than ‘life span’, but we regard that as less illuminating for the reader.

the technical analyses themselves reveal the influence of those motivations over and above where an objective review of the evidence might lead.

The 1990s ICH debate on the need for lifespan carcinogenicity studies: two species or one?

The very origins of the debate about carcinogenic risk assessment at ICH reveal the primacy of commercial and political interests over solely technical considerations. This is because ICH was supposed to be harmonising different techno-regulatory standards across various countries and regions of the world, specifically the EU, Japan, and the USA. Yet, by the 1980s, the techno-regulatory standards for carcinogenicity testing in North America, Europe, and Japan were already in harmony, namely, the two lifespan studies in two rodent species, albeit with recognised limitations. Such testing was brought before ICH because significant sections of the pharmaceutical industry, and some regulators sought to *reduce* it under the guise of ‘harmonisation’. Indeed, as we will show, it could be argued that ICH produced *less* ‘harmony’ than existed in the decade preceding its existence.

At ICH, the critics of lifespan carcinogenicity studies contended that several of the mechanisms elucidated for non-genotoxic rodent carcinogenesis caused by pharmaceutical substances did not operate under the conditions of human exposure to the drugs (Monro 1992). According to Monro (1994), this explained why the US National Toxicology Program database did not show a good correspondence between the tissue sites of occurrence of human cancer and the target sites for chemical carcinogens in rodents. For example, cancers of the colon and rectum are rare in rodents, but common in humans, and vice versa for liver and lung cancers (excluding tobacco-related cases). Thus, Monro condemned rodent lifespan carcinogenicity tests for generating too many false-positives, that is, positive carcinogenicity results in rodents for drugs that are not carcinogenic to humans.²

These critics claimed that scientific understanding of the mechanisms involved in such carcinogenesis had increased so greatly that it was possible to distinguish those mechanisms that appear to be specific to the animal model from those that could be reasonably expected to have trans-species, and hence human, relevance (Monro 1994). In so doing, they gave the impression that scientific progress in understanding the mechanisms of cancer had undermined

the validity and relevance of lifespan carcinogenicity testing in rodents for human hazard assessment. However, many scientists expressed an opposing view that the relevance of toxicity findings for humans was increased if the same effect was observed in two or more mammalian species, rather than in one (Parkinson and Grasso 1993; Zbinden 1987, pp. 51–52). Similarly, Schou (1992, p. 210) acknowledged that ‘it is generally agreed’ that the lifespan carcinogenicity study is the test which ‘gives the optimal answer to the question if a new drug presents a carcinogenic risk’. Furthermore, when Monro was asked, at ICH, how he could be sure that there are too many false-positives in rodent lifespan carcinogenicity studies, he replied: ‘I am not certain whether there are too many [carcinogenic] activities ... some of these positives may as yet be unidentified human carcinogens’ (Ekman 1996, p. 298). In other words, some of pharmaceuticals found to be carcinogenic to rodents, which Monro referred to as ‘false-positives’ might, in fact, be carcinogenic risks to humans.

While all agreed that trans-species carcinogens should be distinguished from single-species carcinogens because the former pose a greater risk to human health, critics of lifespan carcinogenicity testing in rodents argued that these distinctions can be made with short-term tests exploring the mechanisms of cancer induction. By contrast, other scientists believe that the existence of trans-species carcinogens underlines the need for lifespan carcinogenicity testing in at least two animal species in order to *identify* them. Without lifespan carcinogenicity tests in two species there is a risk that some trans-species carcinogens will not be identified and that regulators will not have a negative result confirmed in a second species. For these reasons, scientists at the US National Institute of Environmental Health Sciences and the National Toxicology Program recommended that life span carcinogenicity studies should be conducted in at least two animal species and that ‘in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans’ (Fung et al. 1995, p. 682).

Despite the evident scientific uncertainty and range of views about the validity of life span carcinogenicity studies and whether they should be conducted in one or two rodent species, as early as 1992, the ICH expert working group on safety appeared to prejudge the matter by recommending that ‘worldwide guidelines [should] specify the rat as the rodent species to be used in the study for carcinogenic potential’ (Emmerson 1992, p. 208). This signalled the methodological, and arguably political, strategy of many experts at ICH, namely, to provide a techno-scientific justification for the elimination of the lifespan carcinogenicity test in mice as a regulatory standard for new drugs.

² In this context, a positive carcinogenicity finding refers to an experimental result implying that the pharmaceutical compound in question induced tumours and/or cancer in the test animal (mouse/rat), while negative findings refer to results implying no such cancer induction.

Life span mouse studies were more vulnerable to attack because they were strongly suspected to provide weaker predictions of human carcinogenic risk than rats. The ICH expert working group on safety, it seems, had adopted the commercially motivated goals of the industry-funded Centre for Medicines Research. A further indication of the political nature of the strategy is that it did not rest on a consensus within the scientific community. Indeed it was inconsistent with the published conclusions drawn by other expert scientists at that time. Scales and Griffin (1992, p. 138) found that ‘based upon statistical evidence alone the use of only one rodent species for the assessment of the carcinogenic potential of non-genotoxic agents cannot be recommended’. In addition, in a survey of carcinogenicity studies of 22 pharmaceuticals in rats and mice, Bentley et al. (1992) reported at least 10% of the true human carcinogens in the sample of rodent carcinogens were detected by *mouse-only* carcinogenicity findings, i.e. not detected by the rat studies.

Nevertheless, between 1992 and 1996, the ICH entrusted the US Pharmaceutical Research and Manufacturers Association (PhRMA), whose member companies had a commercial interest in cutting drug development times and costs, with the task of co-ordinating a systematic collection of evidence that could justify the conviction that the lifespan carcinogenicity test in mice could be dropped from regulatory requirements (Hayashi 1994). Under the auspices of ICH, a retrospective survey of databases of pharmaceuticals tested in both mice and rats, with a positive result in at least one of the two rodent species, was conducted. The databases consulted were those of the Japanese Pharmaceutical Manufacturers Association (JPMA), the Food and Drug Administration (FDA), the Dutch and German regulatory agencies, and the CMR.³ The ICH used these databases to examine the extent to which: (1) tumour findings in mice gave rise to regulatory decisions against approval or marketing of pharmaceuticals; (2) mouse studies were needed to interpret positive tumour findings in rat studies; and (3) negative findings in mouse studies were ignored in the face of positive findings in rat studies (Van Oosterhout et al. 1997, p. 8).

In their review of the Dutch and German regulatory databases, the ICH experts found that 13 out of 181 pharmaceuticals generated tumours in mice but not rats. Eight induced liver tumours; three caused tumours in the

lung, and three induced mammary tumours. For only one of these 13 compounds (8%) did the positive mouse findings lead to regulatory action. In all other cases, the Dutch or German regulators had judged that ‘the findings *appeared* to be species-specific, not occurring in rats, and therefore *probably* [emphases added] not relevant to humans’ (Van Oosterhout et al. 1997, p. 10). Ten of the 41 pharmaceuticals (25%), which generated tumours in rats, but not mice, led to regulatory withdrawal from, or restriction on, the market. This implies that, in Germany and The Netherlands, positive carcinogenicity findings in rats triggered about three times as much regulatory significance as positive findings in mice.

Regarding the regulatory impact of negative tumour site findings in mice, when there was a positive rat study, it was found that for 40% (27 of 70) of these cases the Dutch or German regulatory assessments gave some weight to an argument that the absence of tumours in mice in the same organ indicated that the tumour findings observed in rats were probably not relevant to humans. The ICH experts interpreted this (40) as a low percentage⁴ and consequently, considered it to be further evidence that mouse studies were of little regulatory significance (Van Oosterhout et al. 1997). Regarding the 14 trans-species rodent carcinogens in the database, it was found that regulatory judgements were usually based on considerations other than the fact that tumour sites in mice corresponded to those in rats, such as: mechanism of cancer induction assumed to be rodent-specific; over-sensitivity of rodents to liver tumours; sufficient safety margin because tumours generated only in high doses in the rodents (Van Oosterhout et al. 1997, p. 15). In other words, the Dutch or German regulators had explained away the trans-rodent-species carcinogenicity findings as not relevant to humans. The validity of so doing is not beyond question. According to some expert toxicologists, ‘it would not be safe to assume that species barriers are never crossed or that there are invariably threshold levels below which non-genotoxic carcinogens pose no hazard for man’ (Roe 1992, p. 105).

Nonetheless, ICH experts reported that the German and Dutch regulatory authorities did not pay any special attention to the fact that a compound increased tumour incidence in both species, rather than just one, when assessing carcinogenic hazard to humans. Consequently, the overall conclusion reported to ICH regarding these Dutch and German regulatory databases was that ‘the relevance of the carcinogenicity study in mice was low’ and that one carcinogenicity study in the rat would be sufficient (Van Oosterhout et al. 1997, p. 16).

³ The data reviews from the Japanese Pharmaceutical Manufacturers Association and the UK industry-funded Centre for Medicines Research related only to industry knowledge of drug development before full regulatory review. Consequently, no analysis of that data independent of industry had been conducted, which raises fundamental methodological limitations. For that reason, most of our discussion concerns the databases and regulatory positions analysed by the European regulators and the FDA.

⁴ We would suggest that 40 per cent could equally be regarded as quite a high percentage, and that ICH’s interpretation of it as low was arbitrary.

It might be suggested that, based on the above findings, it was not in the commercial interests of the pharmaceutical industry to test its drugs solely in rat instead of two tests in the rat and mouse because a second study in the mouse gives drugs, which are found to be ‘positive’ for carcinogenicity in the rat test, a second chance to be ‘negative’. However, that suggestion, though worthy of some consideration, is not the case for two principal reasons. The first long-term and strategic reason is that senior officials in the pharmaceutical industry viewed the elimination of the lifespan carcinogenicity studies in mice as a *first step* to eliminating all such lifespan studies. If the industry shied away from the opportunity to jettison the lifespan studies in mice as a regulatory requirement, then it could never hope to achieve its larger policy reframing agenda, namely the abolition of all lifespan rodent carcinogenicity studies. Secondly, in the short-/medium-term, it is important to understand that ICH was working to establish *minimum* techno-regulatory standards. No longer *requiring* pharmaceutical firms to conduct a second-species life span carcinogenicity study in mice did not mean that a company could not choose to conduct such a study in the aftermath of a positive carcinogenicity finding in mice. Hence, a firm’s drug could still have a second chance of being ‘negative’ for carcinogenicity with a life span mouse study if the company chose to make that investment.

The results of the review by the Japanese Pharmaceutical Manufacturers Association and the Centre for Medicines Research of 178 pharmaceuticals in their databases indicated that positive tumour findings solely in mice had little effect on drugs’ development (Usui et al. 1996, p. 280). This interpretation was based partly on the view that the majority of the ‘mouse-only’ tumours were found in the liver, and the belief that ‘rodent liver tumours have little or no relevance for the assessment of carcinogenic hazard to humans’. Thus, with the support of the Japanese regulators, they recommended that ICH should endorse a reduction in carcinogenicity testing from two rodent species to one, usually the rat (Usui et al. 1996, p. 283).

Representatives of the FDA also presented a retrospective analysis of their database of 125 pharmaceuticals. They reported that 78% of all pharmaceuticals with positive findings in rodent carcinogenicity studies would have been identified by a rat study alone, whereas 64% would have been identified by a mouse study alone. Hence, the FDA’s review of its database for ICH implied that without the mouse study nearly a quarter of the carcinogenic effects from new drugs in their files would not have been detected (Contrera et al. 1997). Furthermore, according to the FDA’s scientific experts at ICH, Contrera et al. (1997), a relatively high proportion of the trans-species carcinogens in the FDA database were either non-approved or approved *with restricted clinical indications related to carcinogenicity*

findings. Evidently, FDA regulators paid special attention to trans-species carcinogens in risk assessment and noted ‘a major regulatory concern’ in relying on a single-rodent-species test because it would not be possible to identify trans-species carcinogens (Contrera et al. 1997, pp. 130 and 138–39).

FDA scientists were also influenced by tumour findings solely in mice and had used them to require manufacturers to conduct additional testing which indicated ‘that compounds were acting through a mechanism which may be relevant to humans’, or ‘even in recommending non-approval of certain agents’ (Ekman 1996, p. 300). DeGeorge noted that he could not say in advance for any given pharmaceutical whether it would be more appropriate to require a single life span carcinogenicity study in rats instead of mice or vice versa, and insisted that ‘you can’t just automatically say “tumours are irrelevant because they are in the mouse or the rat”’ (Ekman 1996, p. 299).

The accounts of these FDA representatives at ICH imply that the Dutch and German regulators seem to have been *more permissive* regarding trans-species rodent carcinogens because, unlike the FDA, they did not give them special weight in risk assessment, even though more precautionary regulation would have warranted such attention. Also, the industry toxicologists and European regulators seem to have been much more willing than the FDA to dismiss liver tumours in mice as irrelevant to human risk. Whereas the FDA noted how tumours in mice, including some of the liver, were significant in such regulatory assessment.

In particular, the interpretation of mouse tumours by the Dutch and German regulators is suggestive of a permissive, rather than precautionary, approach to carcinogenic risk assessment. Consider the fact that in only 1 out of the 13 (8%) mouse-only carcinogens in the Dutch–German pharmaceutical database did the positive mouse finding count against the negative carcinogenicity results in rats and lead to regulatory action. By contrast, 27 of the 70 (40%) of the negative tumour site findings in mice were utilised to count against positive carcinogenicity results in rats. In other words, this suggests that when a carcinogenicity study in mice was positive, but the rat study negative, the former was almost always discounted by the Dutch and German regulators, whereas when a carcinogenicity study in mice was negative, but the rat study positive, quite often these regulators would entertain arguments which could undermine the positive rat study, by reference to the negative findings in the mouse. In both scenarios, the effect is a regulatory assessment in favour of the drug because of a bias towards an overall negative carcinogenicity assessment.

This raises the *possibility* that the positive carcinogenicity findings solely in mice and the occurrence of trans-species rodent carcinogens have not received much attention from European regulators and industry toxicologists (in Japan and

elsewhere) *partly because of permissive industrial and regulatory practices*, rather than solely because they are irrelevant to human carcinogenic risk assessment. Thus, from the perspective of protecting public health, there was a fundamental flaw in basing new regulatory standards for future carcinogenicity testing on a retrospective analysis of regulators' and industry practices. The ICH was creating *doubly permissive* drug regulation in the field of carcinogenic risk assessment by reformulating past permissive practices into the regulatory standards for the future.

More specifically, the FDA's position implied that the reduction from two rodent life span carcinogenicity studies to a single one in rats could *not* be done without losing important regulatory information which might compromise safety because testing in the mouse *was sometimes, and unpredictably, relevant* to human carcinogenic risk assessment. Hence, the FDA's report to the ICH also threatened to undermine the entire ICH project to reduce life span carcinogenicity testing requirements from two to one study. Although DeGeorge (1996) was concerned that it would not be possible to identify trans-species carcinogens with a single-species carcinogenicity study, he conceded that this important regulatory information may not need to be derived from another *life span* rodent carcinogenicity study. FDA scientists at ICH accepted for regulatory purposes that a single rodent life span carcinogenicity study could be carried out combined with a *new type of short-term in vivo* carcinogenicity study in another rodent species (Contrera et al. 1997). According to senior industrial scientists in Europe and the USA,⁵ who were closely involved with the ICH process, the industry representatives and European regulators were willing to drop the life span mouse study and introduce a new regulatory standard requiring nothing more than just one life span carcinogenicity study in rats. However, when the FDA objected to this, a 'compromise' was struck involving the new short-term carcinogenicity tests, which cost only about a fifth of the life span studies, due to shorter duration and fewer animals, and which many in industry hoped would be required only if the single life span test of the pharmaceutical compound in question turned out to be positive.⁵

From controversy to policy reframing: new genetics and alternative short-term animal studies

The short-term *in vivo* carcinogenicity tests in animals proposed as alternatives to the lifespan carcinogenicity studies involved genetic manipulation to produce rodents,

into which genes (or genetic material called 'alleles') are introduced that are associated with tumour development (known as oncogenes), or in which genes/alleles thought to suppress tumour development, known as tumour-suppressor genes are removed—'knocked out' (Tennant 1996). The first genetically engineered rodents were created in the 1970s as animal models for investigations into disease processes, and this remains their principal purpose (GeneWatch 2002). Regarding drug (and chemical) testing, the rationale for these short-term *in vivo* studies is that the early stages of tumour development, known as 'initiation' can be built into genetically engineered rodents so that carcinogenic effects can be detected in the whole live animal much sooner because only the later stages of carcinogenesis need to occur. On this logic, if a new drug is carcinogenic, then it should be detected fairly quickly by these short-term tests because the initiated animals should develop more cancer tumours more rapidly than the control animals (Schou 1992).

While the idea of introducing these *in vivo* short-term tests into regulatory carcinogenic risk assessment probably originated with Cordaro (1989) at the FDA's Division of Research and Testing, they had the potential to satisfy some of industry's interests in reducing drug development costs and time. This explains why some in the industry regarded their introduction as a tactic towards the ultimate goal of elimination of life span rodent studies.⁵ From the perspective of protecting patients and public health from cancer risks, the crucial issue was how well these short-term *in vivo* tests could detect *non*-genotoxic carcinogens because it was this type of carcinogen for which the lifespan studies screened—screening that ICH proposed to replace, at least in part, with the new short-term *in vivo* tests. By contrast, the capability of the new short-term *in vivo* tests to detect genotoxic carcinogens was of secondary importance because screening for those types of carcinogens already existed with the batteries of short-term *in vitro* mutagenicity tests (CoC 2003; Goodman 2001).⁶

By 1996, the dominant view at ICH was that a new techno-regulatory guideline for carcinogenic risk assessment of pharmaceuticals should be introduced permitting the use of one short-term genetically engineered *in vivo* animal (mouse) test instead of one of the two lifespan studies then required. A proposal to that effect was put forward for 'wider consultation', but this was very limited, especially in Europe, where it took the form of a draft guideline posted by the EU's drug regulatory agency. In the USA, the proposal was published in the *Federal Register*—a measure required of the FDA by the US Freedom of

⁵ Interviews with: Vice President of Clinical Safety, Janssen; Vice President of Drug Safety, Millenium Pharmaceuticals; highly distinguished industry toxicologist involved with ILSI.

⁶ Some argued that the short-term *in vivo* genetically engineered animal models might provide additional information on genotoxicity when a compound's genotoxicity was equivocal from *in vitro* tests (van der Laan and Spindler 2002).

Information Act (FoIA). Consultation was sought apparently as a matter of procedure and only after the ICH had already formed a settled view on how to proceed. Views received contrary to moving forward with the proposed guideline had no impact, and proponents of such views were not invited to join the ICH process. As one regulatory scientist put it, regulatory bodies and their expert advisers outside ICH ‘didn’t have much input’, let alone independent academics, patients and public health advocacy groups.⁷

From the views of some involved in ICH, this very limited level of consultation was not accidental. One industry official stated baldly: ‘we want to keep the lay public out of it’,⁸ while others claimed that consumer organisations were ‘amateurs’ lacking adequate expertise,⁹ and ‘more emotional than scientific’,¹⁰ and that ‘the basic problem of safety is the risk perception of the public’.¹¹ Indeed, at the first ICH meeting in 1991, some anxiety was expressed that the FDA’s commitments to guidelines, which lowered regulatory requirements, might be ‘hampered by some well-known lobbies in the US’, undoubtedly meaning public health advocacy groups (Weissinger 1992, p. 252). This concern to keep ICH plans away from potential public scrutiny and criticism was underlined when senior FDA officials declared to ICH that under their legal obligations of the US FoIA, it might be difficult for them, as US regulators, not to share information with US citizens, even if that information was regarded as confidential by their European or Japanese counterparts. The FDA’s approach to this issue was not to try to persuade their European and Japanese counterparts to be less secretive towards *their* citizens, but rather to explore ways in which they could share such information at ICH without having to divulge it to the general public in the US, as might be required under the FoIA (Anon. 1992, p. 14).

In 1997, the ICH Expert Working Group on carcinogenicity testing reviewed the latest short-term *in vivo* carcinogenicity tests. One with rats, lasting 8 weeks, detected 26 of 31 (84%) chemicals known to be non-genotoxic liver carcinogens in rats from lifespan studies and a second, involving rats for 36 weeks, detected only 4 of 7 (57%) of the non-genotoxic chemicals known to be carcinogenic across a number of different organs from life span studies in rats. The ICH concluded that the short-term

tests in rats had ‘not been fully validated’ and that ‘their utilisation’ was ‘problematic’ (MacDonald 1998; Mitsumori 1998, pp. 266–67). Fundamentally, validation of these short-term *in vivo* tests would mean investigating if they could correctly identify known carcinogens and non-carcinogens. Additionally, Weissinger (1992) argued that validation should include studies conducted to show that tumours previously noted near the end of a life span study are not likely to be missed in carcinogenicity studies of a shorter period.

More importantly, however, were the short-term studies involving genetically engineered mice because it was expected that the typical drug-testing scenario under the new regulatory regime would be a life span study with rats and a short-term mouse study. Three types of genetically engineered mouse tests were outlined at ICH in 1997, namely, those involving: transgenic mice with an oncogene, known as v-Ha-ras, introduced (the tgAC model), ‘knock-out’ mice with the tumour-suppressor gene, known as p53, removed (the p53 model), and transgenic mice with the oncogene, known as c-Ha-ras, introduced (the rasH2 model). All three types typically involved administration of the test chemical/drug to the genetically engineered mouse for 20–26 weeks—much shorter than the life span rodent carcinogenicity studies.

In the tgAc model, carcinogens induce skin tumours and typically test compounds have been applied to the mouse-skin (Sistare et al. 2002). This raised obvious questions about this model’s relevance to the carcinogenic risk assessment of pharmaceuticals, whose intended administration would usually be oral. While some research reported this model’s capacity to identify carcinogens administered orally (Tennant et al. 1995), other scientists were sceptical about why disparate carcinogens would be ‘metamorphosed in the skin’ with ‘the implication that a non-genotoxic male rat bladder carcinogen such as saccharin will be capable of producing skin tumours’ in the tgAC mouse (Ashby 1996). At the ICH meeting in 1997, experts acknowledged that only 23 chemicals had been studied in the tgAC mice and that from this ‘limited experience’ the model was ‘showing positive results with both genotoxic and non-genotoxic chemicals and a lack of complete concordance with [life span] rodent carcinogenicity studies’ (MacDonald 1998, p. 275). The review of the tgAC model by the UK Government’s Expert Advisory Committee on Carcinogenicity (CoC) was more forthright, stating: ‘there are insufficient data regarding the mechanisms of tumour induction in this model to assess the biological significance of such tumours’ (Department of Health 1997, p. 115).

The other two models do not imply carcinogenicity by inducing solely skin tumours. Regarding the ‘knock-out’ p53 mouse model, ICH reported that just nine compounds had completed evaluation using this model, resulting in

⁷ Interview with ‘representative’ of the UK Department of Health’s Committee on Carcinogenicity.

⁸ Interview with Vice-President of Clinical Safety, Janssen Pharmaceuticals.

⁹ Interviews with Managing Director of Safety Assessment, Astra Chamwood; senior UK industry toxicologist.

¹⁰ Interview with Director of Toxicology, Pharmacia & Upjohn.

¹¹ Interview with Vice-President of Regulatory Affairs, Hoechst Marion Roussel.

positive detection of the four chemicals tested that were genotoxic carcinogens in lifespan rodent studies, but no detection of the five non-genotoxic carcinogens (MacDonald 1998, p. 276). The CoC concluded that there were insufficient data on the mechanism of chemically induced tumours in these [p53 knock-out] mice' (Department of Health 1997, pp. 114–116). As for the rasH2 model, it detected 17 genotoxic carcinogens but regarding the five non-genotoxic carcinogens tested, in only four was any carcinogenicity detected, and this was from increased tumours in the lung or forestomach only (Mitsumori 1998). ICH experts surmised that this mouse model 'might be used for detection of non-mutagenic carcinogens', but that 'further validation studies were required before drawing a final conclusion' (Mitsumori 1998, p.270). The CoC was more damning, commenting that there was 'no acceptable mechanistic rationale for the use of this mouse model to screen for potential human carcinogens' (Department of Health 1997, p. 115).

Overall, regarding these short-term in vivo tests, the ICH experts made optimistic pronouncements about their promise to detect pharmaceutical carcinogens but noted that 'conclusions cannot be drawn [about their utility] until the results of validation studies are obtained' (MacDonald 1998, p. 272). In view of the results, the CoC reasonably concluded that these short-term tests 'could be useful research tools in evaluating specific carcinogens, but not for use in regulatory screening for potential human carcinogens' (Department of Health 1997, p. 115).

Despite the many concerns about the appropriateness, efficacy, and validity of these new short-term tests, expressed by experts within ICH itself, as well as other institutions, in July 1997, the ICH approved the guideline (S1B), 'Testing for Carcinogenicity of Pharmaceuticals', which proposed that in place of a second life span carcinogenicity study, a short-term study in a rodent model may be appropriate (Lumley and Van Cauteren 1997). This was then transposed into pharmaceutical regulation around the world, especially in the EU, Japan, and the USA, which permitted drug firms to conduct lifespan carcinogenicity studies in just one rodent species so long as they also employed one of these short-term in vivo tests appropriately, even though validation processes, let alone the achievement of validation, did not begin until after 2000 (IFPMA 2000, p.7). The ICH, and its secretariat, IFPMA, declared that such streamlining of testing requirements would accelerate pharmaceutical innovation and patients' access to innovative medicines, thus motivating a perspective that the streamlining was in the interests of patients, regulators, and industry.

Nevertheless, the incoherence of introducing a worldwide 'technical' guideline, come regulation, before its validation when expert scientists acknowledged that such

validation was necessary to support the guideline's scientific integrity did not go unnoticed. For example, the CoC commented that the S1B guideline 'lacked appropriate scientific rigour to justify its use as a working document in the provision of information to support regulatory decisions' (Department of Health 1997, p. 113). One UK drug regulator remarked that 'it was bad science to include an unvalidated assay as an alternative',¹² while one UK scientist from industry poignantly summarised the difficulty of defending ICH's 'technical' approach as science, rather than the expression of industrial and political interests:

I've always been taught, as a scientist, that you don't use anything until you've got some confidence in it, based on a validation. Does it do what you think it's supposed to do? And have you objectively validated that? And there are various criteria you can work through to that—scientifically. And yet in this case [transgenics] there's no real database. Somebody had an idea that they could or should do this [transgenics]. Fine, that's a nice hypothesis, but it wasn't a proven hypothesis.¹³

Organised interests and science as policy rationalisation

Having permitted the US Pharmaceutical Research and Manufacturers' Association (PhRMA) to orchestrate the review of the utility of lifespan carcinogenicity tests, and the International Federation of Pharmaceutical Manufacturing Associations (IFPMA) to be the secretariat of ICH, the international community of government regulatory agencies proceeded to allow the validation of short-term in vivo test to be conducted by the industry-dominated International Life Sciences Institute (ILSI) in the 2000s. The driving forces behind the ILSI validation studies were senior scientists from American pharmaceutical firms, such as Schering-Plough, Sanofi Sterling Winthrop, Novartis, Johnson & Johnson, Merck, and Pfizer.¹⁴ These ILSI validation tests became known as the 'Alternative to Carcinogenicity Testing (ACT)' study. The ACT study sought to validate mainly the genetically engineered animal (mouse) models developed and discussed at ICH, though a couple of other mouse models were added.

Although ILSI was supported by industry membership, it also included collaboration with academic and government

¹² Interview with 'representative' of the UK Medicines Control Agency, now known as the Medicines and Healthcare Products Regulatory Agency.

¹³ Interview with Astra Zeneca toxicologist involved with the ABPI.

¹⁴ Interviews with former UK academic Professor of Toxicology involved with ILSI; Highly Distinguished Industry Toxicologist involved with ILSI.

scientists. However, much more importantly, the steering group for the ACT study, together with its subcommittees, were industry-dominated (Cohen et al. 2001). Such dominance is partly explained by the fact that the pharmaceutical industry funded much of the ACT study.¹⁵ Not only was the ACT study industry-dominated but it also included a large involvement by the same industry scientists who had been central to the development of the short-term in vivo tests at ICH. This was not without consequence regarding the objectivity of the approach to the ACT study. According to many scientists from academia, industry and government, including some closely involved with the ICH process, ‘the ILSI study was an attempt by the industry to convince themselves that these assays [short-term in vivo tests] were not overly sensitive’, that is, they would not produce false-positives by mis-identifying non-carcinogens as carcinogens.¹⁶ Other experts, who did not share this industry agenda and tended to classify many more chemicals than industry as human carcinogens, such as those at the WHO’s International Agency for Research on Cancer (IARC), were not encouraged to participate.¹⁷ Yet, from the perspective of having carcinogenicity tests with the primary purpose of protecting public health, the main concern is that the new tests should not produce false-negatives by failing to identify human carcinogens.

The dominant industry concern to check that the short-term in vivo tests did not produce more false-positives than the rodent life span tests resulted in most of the compounds selected for the ACT study being non-carcinogens. Of the 21 compounds used, only six were human carcinogens, while 15 were non-carcinogens in humans. Thus, the ACT study gave over twice as much attention to checking the validity of these short-term in vivo tests according to industry interests (not too many false-positives) compared with the interests of public health protection (not too many false-negatives). Moreover, the lack of independence of management of the ACT study, evident from industry and ICH dominance, was compounded by the fact that the validation process was not blinded in accordance with the norms of scientific trials. In other words, the scientists/pathologists examining the genetically engineered animals (and their tumours) knew the carcinogenicity status of the compound to which the animal model had been exposed.

As one scientist reflected, the lack of blinding permits the power of suggestion, which was likely to need little encouragement in a context of such an industry and ICH-driven agenda:

So you got this chemical, you get some squiffy data in the main [lifespan] animal studies, you then do a transgenic test and it comes out positive or negative because you say “of course it was positive, we’ve got this bit here, this bit there, that bit there”. Or if it came out negative, you’d say, “well, of course it was negative because these positive things are just artefacts, it was negative here, here and there”. That’s what happens [without blinding], it’s the way people behave. So it has to be done blind, they have to not know what the outcome is going to be, in my view, for a proper study. So as a validation study, it was very badly flawed.¹⁸

Although the ACT study involved only 21 compounds, some compounds were tested in more than one animal model. Across the six known human carcinogens involving 32 tests, the short-term in vivo animal models correctly identified these carcinogens in only 17 (53%), produced nine false-negatives (28%), and 6 (19%) of the results were equivocal. Hence, nearly half of the time, these animal models failed to identify human carcinogens, which does not inspire confidence in their capability to screen for the human carcinogenicity of pharmaceuticals in drug regulation. By contrast, the animal models in the ACT study correctly identified 83% of compounds that were both human non-carcinogens and rodent carcinogens and 100% of the compounds that were non-carcinogens in both humans and rodents (Eastin et al. 2001; Storer et al. 2001; Usui et al. 2001; van Kreijl et al. 2001).

The pharmaceutical industry found these reassuring and became more comfortable about the prospect of using the short-term in vivo animal models. From the perspective of powerful industrial and regulatory institutions, together with their associated expert elites, a method had been found to manage new drugs through the carcinogenic risk assessment part of the regulatory process and perhaps on to the market faster and cheaper for industry and with less workload for regulators. Now that there was confidence that the new short-term in vivo genetically engineered mouse-models did not produce excessive false-positives, their introduction was firmly in the commercial interests of industry and in the political interests of regulators, who had redefined the mission of regulation as the rapid processing of drug development. However, as many scientists acknowledged, the evidence that these new short-term in vivo

¹⁵ Interview with Former Associate Director of Toxicology and Pharmacology at FDA.

¹⁶ Interviews with Vice-President of Safety Assessment, Novartis; Government scientist leading Transgenic Carcinogenesis Group at Laboratory of Molecular Toxicology at the US National Institute of Environmental Sciences; Dutch scientist at the Laboratory of Toxicology, Pathology and Genetics at the Netherlands National Institute of Public Health and Environment; Director of National Center for Toxicogenomics at the US National Institute of Environmental Sciences.

¹⁷ Interview with Industry scientist involved with ILSI ACT.

¹⁸ Interview with academic scientist and former member of the UK Committee on Carcinogenicity.

mouse tests offered any improvement over, or could even adequately replace, the life span studies in mice as means to screen for potential non-genotoxic human carcinogens in the regulatory protection of public health was not forthcoming, given a mere 53% detection rate.

For example, upon reviewing the ACT study and specifically focusing on whether these new short-term in vivo test models using genetically engineered mice could replace lifespan mouse studies, the CoC concluded that ‘none of the models’ were suitable in that regard. Many other scientists also acknowledged this,¹² one by noting that ‘we haven’t solved the problem of non-genotoxic carcinogens’.¹⁹ Even the ACT study scientists acknowledged that among themselves there ‘was not a [scientific] consensus that any individual [genetically engineered mouse] model presents any particular mechanistic advantage over the traditional mouse strains for evaluating chemicals operating through non-genotoxic modes of action’ (Pettit 2001 p. 191). The contradiction inherent in these experts’ efforts to make the techno-science fit their industrial and political goals is perhaps encapsulated in their comment that ‘although they consider the [new genetically engineered mouse] models scientifically valid, the current data set is not sufficient to validate the models’ (Pettit 2001, p. 195).

Discussion and conclusion

As in many areas of techno-scientific uncertainty, controversies over the validity of knowledge-claims and the appropriate interpretation of evidence can be generated by social interests to provoke reframing of policies across networks of institutions and actors (Laws and Rein 2003). However, in this case, we suggest that the government drug regulatory agencies have too readily adopted a narrow industrial agenda of streamlining carcinogenic risk assessment of pharmaceuticals, at the expense of prioritising the interests of patients and public health. This has occurred, despite the fact that government drug regulatory agencies are supposed to regulate the industry on behalf of the public. It is from this latter function that government drug regulatory agencies draw their democratic legitimacy. For this reason, the reframing of carcinogenic risk assessment of pharmaceuticals has been presented as scientific progress and perhaps genuinely accepted as such by many participants, even though there was inadequate technical evidence to support that view in connection with either ICH or ILSI ACT. The extent to which such reframing has been characterised by claims to scientific progress acting as political legitimacy was particularly acute because ICH and ILSI ACT

were industry-dominated, and involved minimal democratic accountability of either regulatory or industry institutions. Indeed, even accountability of the techno-science to the wider scientific community was also rather limited.

The ICH management of the regulatory standards for carcinogenicity testing was about *reducing* testing requirements, rather than the harmonisation of inconsistent standards across regions. Indeed, one could argue that ICH produced *less* ‘harmony’ than existed before because of the difference of opinion between FDA scientists and European regulators about the value of carcinogenicity studies in mice. Three mutually supporting reasons suggest that the ICH’s approach to the lifespan carcinogenicity test in mice reflected permissive regulation leading to a *diminution in safety standards to protect public health*.

Firstly, the ICH analysis was based on accounts of past practice by industry and regulators, yet there is evidence that this practice was permissive with respect to the regulatory standards of the time because industry and EU regulators were much more dismissive of tumour findings in mice than their FDA counterparts—widely regarded at the time as among the most rigorous regulators in the world. Secondly, the ICH analysis itself revealed that European regulators were much more permissive in regulating trans-species rodent carcinogens than the FDA. A much lower proportion of trans-species carcinogens were non-approved or restricted by EU regulators, than by the FDA. And thirdly, a fivefold higher percentage of negative carcinogenicity findings in mice was used by European regulators to suggest that positive carcinogenicity findings in rats were irrelevant to human safety, than have positive carcinogenicity findings in mice been used to suggest that negative carcinogenicity findings in rats may be wrong.

Consequently, there is reason to believe that ICH converted permissive regulation into new scientific standards for carcinogenic risk assessment. It is difficult to see how this could not lower safety standards unless the new short-term genetically engineered in vivo animal tests proved to be breakthroughs. Significantly, however, the ICH guideline to reduce lifespan carcinogenicity testing was accepted by regulators in the EU, USA, and Japan by 1998—before validation of those new short-term tests was completed. When a validation process finally took place, it again prioritised industry interests in checking that the new short-term tests did not mis-identify too many human non-carcinogens as carcinogens (false-positives) but failed to provide adequate information about whether the tests could screen for human carcinogens—the most important information needed by regulatory agencies to protect public health from carcinogenic pharmaceuticals. In this respect, the new tests seemed to lack validity, but this had no impact on the maintenance of new loosened techno-regulatory standards.

¹⁹ Interview with senior UK industry toxicologist.

In conclusion, our research suggests that neo-liberal political influences on the regulatory agencies, such as the goal of increasing and accelerating access to markets for industry, are neither neutral nor coincidental in their effects on the regulatory science of carcinogenic risk assessment. Rather, such ideological influences are associated with a loosening of regulatory standards in the area of safety testing. During approximately the last 20 years, this ideology has penetrated the scientific knowledge base of carcinogenic risk assessment itself by first creating a political environment in which a permissive gap between the practices of regulatory scientists and the cognitive norms of their regulatory science has become administratively acceptable, especially in Europe; and then introducing a new worldwide regulatory science in which the cognitive norms have been made more consistent with those permissive practices. Yet, these changes create tensions with the democratic legitimacy of regulatory agencies and public acceptance of the pharmaceutical industry so it has been important for those institutions to present the aforementioned changes to techno-regulatory standards as scientifically progressive so that they can continue to claim a commitment to patient safety and public health protection.

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